REMARKS

In view of the following Remarks, the Examiner is requested to withdraw the rejection and allow Claims 14, 15, 25, 26, and 28-34, as well as newly presented Claim 35, the only claims pending in this application and currently under examination.

FORMAL MATTERS:

Claim 35 is added. Support for this claim is found throughout the specification, for example on page 5, beginning at line 31.

No new matter is added. As such, the Examiner is requested to enter the above amendments.

REJECTIONS UNDER §103(A)

Claims 14, 15, and 25-32 are rejected under 35 USC 103(a) as being unpatentable over Frankel et al. (US Patent No. 6,099,848, issued August 8, 2000) in view of Frazao et al. (WO 99/07861, published 18 February 1999) and Loessner et al. (Molecular Microbiology 35(2):324-340, 2000).

The Applicants respectfully submit that in making this rejection, the Examiner has assumed that one of ordinary skill in the art at the time of the present invention would have believed that attP attachment sites are domains that function as autonomous structures independent of the phage genomes in which they reside and hence could be readily isolated and used to confer integration capabilities on a non-phage DNA molecule. However, the Applicants submit that, in view of the art discussed further below, one or ordinary skill in the art would have had no such beliefs. Accordingly, and contrary to the Examiner's assertions, the ordinary skilled artisan would not have predicted with any reasonable expectation of success that a listeriophage attP site identified in silico by Loessner et al. could provide for an integration vector capable of integrase mediated site-specific Listeria genome integration, which in turn would provide for cells that are transformed with an integration vector capable of integrase mediated site-specific Listeria genome integration as recited by the pending claims.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740

(2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g.*, *KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added . As such, in addition to showing that all elements of a claim were known in the prior art and that one of ordinary skill in the art had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

Claim 14, upon which the remaining claims depend, is directed to a method of eliciting or boosting a cellular immune response to an antigen in a subject, comprising "administering to said subject an effective amount of Listeria cells that express said antigen, wherein said cells are transformed with an integration vector capable of integrase mediated site-specific Listeria genome integration, wherein said integration vector comprises a listeriophage attachment site." Thus, the claims specify that the Listeria cells comprise an integration vector that comprises a listeriophage attachment site and is capable of integrase mediated site-specific Listeria genome integration.

The Applicants submit that Frankel et al in view of Frazao et al and Loessner et al does not render the claims obvious because one of ordinary skill in the art, in view of the art, would not have been able to predict with any reasonable expectation of success that they could generate an integration vector capable of integrase mediated site-specific Listeria genome integration by inserting the attP integration sequence of Loessner et al. into the vector of Frazao et al.

Frankel teaches the attenuated Listeria monocytogenes bacteria. However, Frankel does not teach integration vectors capable of integrase mediated site-specific Listeria genome integration, or how to go about making such vectors. Accordingly, Frankel et al. does not make obvious "wherein said cells are transformed with an integration vector capable of integrase mediated site-specific Listeria genome integration, wherein said integration vector comprises a listeriophage attachment site."

Frazao et al. does not remedy this deficiency of Frankel, because although Frazao et al. teaches that their site-specific integration vectors may be modified to become capable of integration into bacterial genomes other than Mycobacterium spp., Frazao et al. does not teach how to modify their vectors such that they will be capable of integrase mediated site-specific integration into other bacterial genomes, and in particular, into the Listeria genome. Accordingly, Frazao et al. does not make obvious "wherein said cells are transformed with an integration vector capable of integrase mediated site-specific Listeria genome integration, wherein said integration vector comprises a listeriophage attachment site."

Loessner et al. does not remedy this deficiency of Frazao et al., because although Loessner et al. teaches an attachment site sequence for the listeriophage A118, Loessner, like Frazao et al., also does not teach how to modify DNA vectors such that they will be capable of integrase mediated site-specific Listeria genome integration.

Loessner et al. teaches a 3bp core attachment site sequence for integrase-mediated site-specific integration. However, the art teaches the importance of non-core phage DNA sequences in achieving integrase-mediated site-specific integration as well, and that the importance of these non-core sequences varies between phage. For example, Hoess and Landy ((1978) PNAS 75(11):5437-5441) (Exhibit A) teach the importance of phage sequences flanking the 15bp attP core attachment sequence for lambda phage integration. Likewise, Boyce et al. ((1995) Appl. and Environ. Microbiol 61(11):4105-4109) (Exhibit B) teaches that the attP core attachment sequence for the lactococcal bacteriophage BK5-T is a 9bp structure, but also teaches that the "the regions of DNA [surrounds the BK5T core sequence] may be important to binding integrase or an L. lactis IHF homolog" (p. 4108, col. 1, para. 2). In contrast, Cinciotto et al. ((1986) J. Bacteriology 168(1): 103-108) (Exhibit C) teaches that the attP core attachment sequence for β phage is 96bp, and that, based on their results, "very little phage sequence specificity may be required for integration outside the 96-bp sequence shared with the bacterial genome" (p. 107, col. 1, l. 15-33). In view of these differences in the requirements for non-core sequences observed between phage, the ordinary skilled artisan would have believed it unreasonable to expect that a postulated attachment site from any phage would be functional outside the context of a phage genome prior to such a demonstration in the art, and would have had no reasonable expectation of successful site-specific bacterial genome integration from a vector modified to include such an untested attP sequence.

Neither Loessner et al. not any other art at the time of the present invention provides a teaching as to whether, as in β phage, the core attachment site of Listeriophage taught by Loessner et al. would be sufficient to confer upon a DNA molecule the ability to undergo integrase-mediated site specific integration with another DNA molecule, or if, as in lambda and lactococcal bacteriophages, other flanking sequences outside this core attachment site are also required. Accordingly, and contrary to the Examiner's assertions, one of ordinary skill in the art, following the teachings of Loessner et al. in view of the art, would have had no reasonable expectation of success that modifying the vectors of Frazao et al. to include a sequence taught by Loessner would render Frazao's vectors capable of integrase mediated site-specific Listeria genome integration. Thus, Frankel et al. in view of Frazao et al. and Loessner et al. does not teach nor suggest the element of "wherein said cells are transformed with an integration vector capable of integrase mediated site-specific Listeria genome integration, wherein said integration vector comprises a listeriophage attachment site".

In making the rejection, the Examiner asserts that "It would have been prima facie obvious to one having ordinary skill in the art at the time that the invention was made to modify the pAVI of Frazao et al by substituting the integrase gene and attP site of the A118 bacteriophage of Listeria monocytogenes according to Loessner et al. for the attachment site region (attP) and the integrase gene of the mycobacteriophage Ms6 of the pAVI of Frazao et al. . ." (Office Action, May 13, 2009, p. 5, l. 10-14)

The Applicants submit that, in view of the above-described art, an impermissible "obvious to try" standard has been applied by the Examiner in an attempt to argue the obviousness of the claimed invention. The "obvious to try" standard for obviousness was addressed by the Supreme Court in KSR. According to the Supreme Court, "When there is a design need or market pressure to solve a problem and there are a finite number of identifiable, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp" (emphasis added).[1]

[1] *Id.* at 402.

This tenet has been followed in several post-KSR decisions recently published by the Federal Circuit.[2] For example, the Federal Circuit recently explained in *In re Kubin* that "the Supreme Court's admonition against a formalistic approach to obviousness in KSR actually resurrects this court's own wisdom in *In re O'Farrell*. This court in O'Farrell cautioned that 'obvious to try' is an incantation whose meaning is often misunderstood." [3] The Federal Circuit then reiterated the two classes of situations provided in *O'Farrell* where 'obvious to try' is erroneously equated with obviousness under § 103:

> The first class of *O'Farrell's* impermissible "obvious to try" situations occurs where
>
> > what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.[4]
>
> The second class of *O'Farrell's* impermissible "obvious to try" situations occurs where
>
> > what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.[5]

Applicants assert that both classes of impermissible "obvious to try" situations apply to the present case, because, as in *In re O'Farrell*, what the Examiner asserts was "obvious to try" was, in fact, exploration of a general approach that, while a promising field of experimentation, was only supported by general guidance in the art as to how to achieve the particular form of the claimed invention and the art gave no direction as to which of many possible choices (in this case, phage sequences comprising the listeriophage core attachment site taught by Loessner) was likely to be successful .

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[2] *See, e.g., Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008); *Eisai Co. v. Dr. Reddy's Laboratories*, 533 F.3d 1353 (Fed. Cir. 2008); *Pfizer, Inc. v. Apotex, Inc.* 488 F.3d 1377 (Fed. Cir. 2007); *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007).

[3] *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

[4] *Id.* at 1359 (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

[5] *Id.*

The Federal Circuit in *O'Farrell* observed that an obviousness finding was appropriate where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and *evidence suggesting that it would be successful*" (emphasis added).[6] In *O'Farrell*, the Federal Circuit affirmed an obviousness rejection of a claim to a method for producing a "predetermined protein in a stable form" in a transformed bacterial host.[7] The main difference between the prior art and the claim at issue in that case was that the heterologous gene in the prior art was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein.[8] Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, the prior art mentioned *preliminary evidence* that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result.[9] In affirming the obviousness rejection, the Federal Circuit explained that "the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, *and presented preliminary evidence* suggesting that the [claimed] method could be used to make proteins" (emphasis added).[10]

In contrast to the situation in *O'Farrell*, the cited art in this case offers no preliminary evidence suggesting the claimed invention would work. Specifically, neither Loessner et al. or Frankel et al. provide preliminary evidence to teach or suggest that integrase-mediated site-specific genomic integration into Listeria could be achieved by using a listeriophage attP site out of context of the listeriophage genome. Rather, the cited art gives "only general guidance as to the particular form of the claimed invention or how to achieve it." In view of the art at the time of the present invention as exemplified by Cianciotto et al,. discussed above, which teaches away from making any assumptions about the functionality of an isolated attP site, such preliminary evidence would be vital in order for the combination of cited references to render the pending clams obvious. Absent such preliminary evidence, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Thus, the "obvious to try" suggestion of Frazao et

[6] 853 F.2d at 902.

[7] *Id.* at 895.

[8] *Id.* at 901.

[9] *Id.*

[10] *Id.*

al., together with Loessner et al. and Frankel et al., does not render the invention claimed in the present application obvious.

Additionally, Applicants submit that new Claim 35 is also patentable for at least the reasons above.

In light of the above remarks, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number BERK-017CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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Enclosure: Exhibits to accompany response, including:
Exhibit A: Hoess and Landy (1978) PNAS 75(11):5437-5441
Exhibit B: Boyce et al. (1995) Appl. and Environ. Microbiol 61(11):4105-4109
Exhibit C: Cinciotto et al. (1986) J. Bacteriology 168(1): 103-108

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